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Perioperative management of patients undergoing pituitary surgery

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The perioperative management of a patient undergoing pituitary surgery varies according to the size of the pituitary lesion, the type of lesion, the surgical approach (transsphenoidal, craniotomy), and ideally the preoperative endocrine function. Because there is no "one best" method for all patients undergoing pituitary surgery, this article addresses these considerations and the current practices of the Neuroendocrine Center at the University of Virginia [1–5].

The ideal situation for a patient with a pituitary tumor is an adequate endocrine evaluation before the planned operation. An unfortunate fact is that many patients undergo surgery without such an evaluation and the endocrinologist is asked to see the patient after surgery, often on the day of hospital discharge. In this situation the patient is usually receiving a glucocorticoid and the challenge is to determine the need for chronic replacement of this and other hormones. In addition to assessing pituitary function, the endocrinologist must review the anatomic study (MRI, CT), preferably with an experienced radiologist, to evaluate the size, characteristics, and extension of the lesion that cannot be appreciated by reading the radiology report. After surgery, the endocrinologist should review the operative report to ascertain the extent of the surgery (selective removal of a tumor, amount of normal pituitary removed) and the pathology report (presence of posterior pituitary tissue, normal tissue, immunostaining of the adenoma) to correlate these findings with the clinical features and endocrine results. For example, if a large portion of normal tissue is removed then the endocrinologist can anticipate the probable need for multiple hormone replacements.

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General principles

Size of the pituitary lesion

The size of the lesion is important in assessing the likelihood of preoperative and postoperative hypopituitarism. A macroadenoma (> 10 mm) is more likely to compromise normal pituitary function resulting in secondary adrenal insufficiency, hypothyroidism, hypogonadism, and growth hormone deficiency. A pituitary adenoma, regardless of the size, rarely causes diabetes insipidus (DI) before surgical intervention. The MRI is particularly helpful by demonstrating a discrete mass (usually hypodense after gadolinium administration) with a small rim of compressed enhancing normal pituitary tissue, a cystic and solid mass; suggesting a craniopharyngioma, or a diffusely enlarged, homogeneous gland with pituitary stalk thickening (water bottle or triangular shape); suggestive of an infiltrative process such as lymphocytic hypophysitis, sarcoidosis, or a metastatic tumor. Patients with a lesion suggesting a craniopharyngioma or an infiltrative process are more likely to have panhypopituitarism and diabetes insipidus and they have a high probability of developing DI after surgery.

Type of pituitary lesion

The definitive diagnosis of a pituitary lesion resides in the surgically resected specimen with appropriate immunostaining for all of the pituitary hormones. Serum and urine tests can identify the secretory adenomas, prolactin, growth hormone (alone or in combination with prolactin), adrenocorticotropic hormone (ACTH), luteinizing hormone (LH), follicle-stimulating hormone (FSH) or α subunit (alone or in combination) and thyroid stimulating hormone (TSH), the least common type of secretory adenoma. Identification of the type of secretory tumor has implications for perioperative management. For example, patients with Cushing's disease have a higher risk for developing a postoperative pulmonary embolism thus making postoperative physical activity important in these patients. A patient with acromegaly may have difficulty with intubation requiring an awake intubation, difficulty breathing with the nasal packs postoperatively requiring a nasal trumpet, or sleep apnea requiring C-PAP therapy postoperatively. The uncommon patient with a TSH producing adenoma must be identified before surgery and treated for hyperthyroidism to reduce the risk for arrhythmia during surgery.

Surgical approach

The surgical approach, transsphenoidal or craniotomy will influence the postoperative management of steroid administration. Patients who undergo a transsphenoidal resection are usually given intravenous hydrocortisone in "stress" doses (100-mg IV every 6 to 8 hours) that may be tapered rapidly

over 2 to 3 days to physiologic replacement or discontinued if postoperative serum cortisol levels are normal after stopping hydrocortisone. In contrast, patients who require a craniotomy (determined by the size and location of the lesion) are usually given large doses of long acting dexamethasone to reduce the risk for brain edema. In this situation, the ''steroid taper'' is longer, usually over 1 to 2 weeks, thus prolonging hypothalamic–pituitary–adrenal suppression, recovery, and precluding the ability to test for the need for chronic steroid replacement immediately after surgery.

Preoperative endocrine testing

If the patient is seen before surgery, the necessary assessment can be performed in one outpatient visit in all patients except those with suspected Cushing's disease. The history and physical examination often suggest the diagnosis and hormone studies confirm the clinical impression. Symptoms of fatigue, weight loss, dizziness, weakness, and difficulty concentrating suggest secondary adrenal insufficiency. Premenopausal women may have disturbance in menstrual function and men often have diminished libido or erectile dysfunction. A patient who reports frequent nocturia (every 1 to 2 hours) and increased thirst likely has diabetes insipidus. A patient with supraclavicular fat deposition and pigmentation of the knuckles and elbows likely has ACTH dependent Cushing's (does not distinguish between pituitary dependent and ectopic ACTH syndrome).

Baseline endocrine studies should include: serum cortisol and ACTH (preferably in the morning), free thyroxine (FT4), TSH, prolactin, LH, FSH, α subunit, insulin like growth factor-1 (IGF-1) and testosterone (men). A subnormal morning cortisol in the setting of a ''normal'' ACTH level indicates secondary adrenal insufficiency and the need for glucocorticoid replacement. A low free T4 level in the setting of a ''normal'' or suppressed TSH indicates secondary hypothyroidism (TSH should never be measured as the sole test to assess thyroid function in a patient with possible or diagnosed pituitary disease). Additionally, an elevated free T4 in the setting of a ''normal'' or increased TSH indicates a TSH producing adenoma and the need to treat the hyperthyroidism before surgery. Serum prolactin is necessary to diagnose a prolactinoma and the level must be correlated with the anatomic findings. In patients with a macroadenoma (tumor >1 cm), the serum prolactin should be greater than 200 μg/L (ng/mL) to consider this a true prolactinoma, thus indicating medical, not surgical, therapy. Many patients with a macroadenoma have a mild elevation of prolactin (40–100 μg/L [ng/mL]) because of interference with dopamine inhibition of lactotrope cells (''stalk effect''). One caveat regarding the measurement of serum prolactin is that most laboratories use an automated method in which the upper limit of measurement is around 190 to 200 μg/L (ng/mL) and may report the value as ''190'', ''200'', or ''>200''.

This type of report is misleading unless the sample is diluted; a value of >200 may be 201, 2000, or 20,000 μg/L (ng/mL). When evaluating a new patient, the serum prolactin should be ordered as "neat and diluted" to alert the laboratory that a precise value is necessary. Serum LH, FSH and α subunit are measured to determine if a gonadotrope tumor is hypersecreting one or more of these hormones, thus providing a "tumor marker" to assess the effect of surgery. Serum IGF-1 should be measured in every patient for two reasons: (1) a patient with hyperprolactinemia may also have excessive growth hormone (GH) secretion without classical features of acromegaly and (2) a low serum IGF-1, particularly in the setting of other pituitary hormone deficiencies, likely indicates GH deficiency which should be properly assessed with a stimulation test after surgery. The first reason is more important—a patient with a true prolactinoma should be treated medically with a dopamine agonist drug and a patient with excessive prolactin and GH secretion should undergo surgery as the first therapy.

The question of the need for dynamic tests before surgery often arises in a patient with a pituitary lesion. Whereas it is desirable to know if there is diminished ACTH reserve (optimally assessed with an insulin hypoglycemia test), practically, this is not necessary if the patient is to undergo surgery. The most important time to assess hypothalamic–pituitary–adrenal function is after surgical resection to determine the need for chronic steroid replacement and to diagnose GH deficiency. Hypothalamic-pituitary-adrenal function is best assessed postoperatively by the insulin hypoglycemia test, which is the most accurate method to determine the need for chronic steroid replacement, and for GH replacement. Preoperative administration of GnRH and TRH are not necessary because gonadal function and the need for thyroid hormone replacement will need to be assessed after surgery and can be determined by measurement of serum testosterone in men, return or absence of menses in premenopausal women, and measurement of the total thyroxine or free T4 level after surgery. The only necessary preoperative dynamic test is in a patient with acromegaly, the oral glucose tolerance test, is valuable to confirm the diagnosis and to provide a pre-surgical assessment of GH suppression by glucose for comparison of postoperative values. This test is not absolutely necessary before surgery in a patient with clinical features of acromegaly, an elevated serum IGF-1 and a pituitary lesion, but is helpful for comparison of glucose suppressed GH levels after surgery. For practical purposes, dynamic tests before pituitary surgery are not necessary except in patients with suspected Cushing's disease. The most important assessments are to determine the need for glucocorticoid and thyroid hormone replacement before the patient undergoes the stress of anesthesia and surgery; the need for other hormone replacements should be determined after resection of the pituitary lesion.

If there is a clinical concern of Cushing's syndrome, the most reliable screening test is measurement of the 24-hour urine free cortisol (UFC) and

creatinine concentrations using a reliable assay (some laboratories still use an outmoded method of measuring UFC by radioimmunoassay which may produce false elevation of UFC). If the 24-hour UFC concentration is elevated and the serum ACTH is "normal" or elevated, then dynamic tests including a low dose dexamethasone suppression test or a low dose dexamethasone suppression test with CRH administration (to establish the diagnosis of Cushing's syndrome), a high dose dexamethasone suppression test (for the differential diagnosis of ACTH dependent Cushing's), and inferior petrosal sinus sampling (IPSS) with CRH administration (the most reliable test to exclude ectopic ACTH) are appropriate studies. Because none of the dynamic endocrine tests (dexamethasone tests) for suspected Cushing's disease are 100% sensitive or specific, the definitive test is the IPSS test with CRH administration and measurement of petrosal and peripheral ACTH concentrations. This should be performed by an experienced interventional radiologist and the ACTH samples must be processed immediately after the study to obtain reliable values. Although the diagnosis of other pituitary lesions and the need for hormone replacement can be made in a single setting, patients with suspected Cushing's disease require additional studies to confirm the clinical impression.

Preparation for surgery

There is probably no one "best" regimen for the perioperative care of the patient undergoing pituitary surgery. There are several principles that most endocrinologists who care for such patients would agree on. Unless there is an emergency or urgency for surgery (visual loss, cranial nerve palsy, and apoplexy), the surgical schedule is not set in stone. Recalling that a patient with a pituitary adenoma has likely had the lesion for a considerable time (often years) before diagnosis, eventual diagnosis does not constitute a need for immediate surgery that precludes appropriate pre operative endocrine evaluation and treatment. Again, the surgical schedule is not the primary determinant of the appropriate date of surgery unless there is visual loss. Glucocorticoid and thyroid hormone replacement and control of diabetes insipidus are the most important hormone replacements to institute before surgery. If thyroid hormone replacement is given to a patient with impaired ACTH reserve, this may precipitate an adrenal crisis, emphasizing the need to assess the need for glucocorticoid replacement before giving thyroid hormone replacement. Replacement of gonadal steroids and growth hormone should be assessed and prescribed after surgery as indicated by appropriate studies.

The traditional method of preparing a patient for pituitary surgery is to administer "stress doses" of hydrocortisone to all patients, usually hydrocortisone 100 mg every 6 or 8 hours intravenously. Some centers continue steroid treatment during the postoperative period and discharge

patients on steroid replacement with plans to assess hypothalamic–pituitary–adrenal function at a later date. In our institution patients with Cushing's disease are not given a glucocorticoid at the time of surgery and the serum cortisol level is measured every 6 hours for 3 days following surgery. This is possible because the laboratory provides almost immediate results (automated assay that requires < 1 hour to complete). This allows immediate assessment of the surgical results and the need for steroid replacement. The ideal result in a patient with Cushing's disease is a serum cortisol of < 2 μg/dL with symptoms of adrenal insufficiency at which time hydrocortisone replacement is given.

In our patients with other types of pituitary lesions, hydrocortisone, 100 mg, is given intravenously before surgery and every 6 hours for 24 hours (total of 5 doses). On the following 2 days of hospitalization a morning serum cortisol is measured. If the morning serum cortisol is > 10 μg/dL and the patient feels well, the patient is discharged on no steroid replacement, but is given a prescription for hydrocortisone, 20 mg on awakening and 10 mg at 6 pm. The patient is also given telephone numbers to contact the Neurosurgery and Endocrine services if there are any problems or symptoms of adrenal insufficiency. Patients who have secondary adrenal insufficiency before surgery are instructed to continue steroid replacement after discharge from the hospital. Hydrocortisone is withheld for 24 hours before the postoperative visit with measurement of serum ACTH and cortisol during the visit. Dynamic testing (insulin hypoglycemia test), as indicated, is performed at a later date. Because 9% of patients develop transient hyponatremia (SIADH) 8 to 10 days after surgery and the symptoms are virtually identical to those of adrenal insufficiency (patient reports feeling ill, nauseated, with headache or anorexia), the patient is asked to have a serum sodium and serum cortisol measured immediately at the local physician's office or emergency room with results telephoned to the service. If the serum sodium is low and the patient is symptomatic, a brief hospitalization with fluid restriction (500–800 mL/24 h) is indicated until the serum sodium is normal. If the serum cortisol is < 10 μg/dL, hydrocortisone is administered with the need for chronic steroid replacement assessed at the 6 week postoperative visit.

Postoperative hormone deficiency

Approximately 6% of patients with preoperative pituitary deficiencies will experience some recovery of pituitary function. Although recovery of pituitary function after surgery is unlikely, it is still appropriate to determine the need for continued hormone replacements.

In our institution, patients who were given postoperative hydrocortisone replacement are instructed to withhold the medication for 24 hours before the postoperative visit (usually 6 weeks after surgery) and serum ACTH and

cortisol levels are measured. The patient is instructed to bring the medication to the clinic visit and take the usual dose after the blood is obtained pending the results of the tests. The need for chronic glucocorticoid and growth hormone replacement is assessed at a later date with an insulin hypoglycemia test (ITT). In the patient with preoperative and postoperative panhypopituitarism (morning serum cortisol < 10 μg/dL at the postoperative visit, off of hydrocortisone for 24 hours or more), diabetes insipidus and a history of a large tumor, the ITT may be excluded and another test, such as L-arginine or L-arginine + growth hormone releasing hormone (GHRH), is adequate to confirm the suspicion of growth hormone deficiency. The insulin hypoglycemia test (ITT) is contraindicated in patients with coronary artery disease, seizure disorder or generalized debility.

Transient postoperative diabetes insipidus (DI) occurs in approximately 12% of patients, with this being permanent in 3%. The patient with a craniopharyngioma, Rathke's cleft cyst, sarcoidosis, lymphocytic hypophysitis or metastatic disease is at risk for permanent DI because of involvement of the pituitary stalk. Patients with a large pituitary adenoma are more likely to develop postoperative DI than those with an intrasellar tumor (presuming that the stalk was not damaged). To determine if the patient requires chronic desmopressin (dDAVP) replacement, the medication should be withheld periodically (usually once a week for 3–4 months)—if there is no nocturia then the desmopressin can be discontinued. It is uncommon to require a formal water deprivation test. Once the nasal stuffiness and accompanying dry mouth causing increased oral fluid intake resolves (usually takes 4–6 weeks), the diagnosis of DI can be made by asking about nocturia—the patient who urinates every 1 to 2 hours during the night has DI and requires replacement. The patient who sleeps through the night or who urinates once a night does not usually have DI.

The need for gonadal steroid replacement should be determined well after surgery. Resumption of menses in premenopausal women usually occurs 3 to 4 months after surgery. If this does not occur then cyclic estrogen and progesterone replacement is indicated. Women who desire fertility should be informed that pregnancy is possible with administration of gonadotropins to achieve ovulation. In men, report of libido and erectile function and measurement of serum testosterone are used to determine the need for testosterone replacement. It is prudent to measure a serum PSA before recommending testosterone replacement in men over 40 years and following the PSA level yearly in men who are given testosterone.

If the patient was placed on thyroid hormone replacement before surgery, the only way to assess the need for chronic replacement is to discontinue thyroid hormone and measure the serum thyroxine or free T_4, optimally 6 to 8 weeks after discontinuation, because of the long serum half life of thyroxine. Measurement of serum TSH is of no value to assess the need for replacement because the TSH is usually in the "normal range" in the setting of secondary hypothyroidism.

Postoperative complications

Cerebrospinal fluid leak

The most potentially dangerous complication of pituitary surgery is development of a cerebrospinal fluid (CSF) leak, which may occur days to weeks after discharge from the hospital. Symptoms include persistent drainage of fluid from the nose, usually clear fluid. More concerning symptoms include headache and fever suggesting meningitis. Patients at greatest risk for developing a CSF leak are those who had a large tumor and who required a fat graft to fill the space after tumor removal. Diagnosis of a CSF leak is clinical and aided by measuring glucose in the nasal fluid. A more reliable test is measurement of ατ-transferrin (a protein found in the CSF) in the nasal fluid. A positive test indicates a CSF leak requiring immediate neurosurgical evaluation and treatment (usually surgical repacking of the sella, a lumbar drain and antibiotic therapy). Unfortunately, the ατ-transferrin test may not be immediately available in some hospitals, thus delaying a definitive diagnosis. If there is a concern about a postoperative CSF leak, the neurosurgeon should be contacted immediately to evaluate and treat the patient and for appropriate antibiotic administration.

Assessing cure (remission)

Although it is ideal to consider the result of surgery in terms of cure, it is more realistic to consider the outcome in terms of remission. The reported incidence of tumor recurrence varies according to the type of tumor, ranging from 12% for Cushing's disease, 16% for a nonfunctioning adenoma, and up to 50% for a prolactinoma. Thus, it is prudent to refer to the optimal outcome of surgery as remission with the need for lifelong monitoring for recurrence.

Remission in a patient with a nonfunctioning adenoma or craniopharyngioma is defined as no visible lesion on the postoperative MRI study and no increase in size of remaining tissue over time. Because there is no "tumor marker" as occurs in patients with a secretory adenoma, these patients must be followed with a yearly MRI study for the first 5 years after surgery. If there is no evidence of recurrence, the interval between MRI studies may be extended to every 2 years. The patient should be instructed to immediately report any new onset of headache or visual disturbance between scheduled visits. Because tumor recurrence may occur 20 or more years after surgery, these patients require life-long monitoring.

Remission in a patient with a secretory adenoma involves assessing hormone production by the specific tumor cell type. As noted, the optimal outcome in a patient with Cushing's disease is a postoperative serum cortisol of < 2 μg/d, the need for steroid replacement and clinical improvement. In the patient with Cushing's disease who requires steroid replacement, the

question is how long steroid replacement will be required. This is variable and may range from a few weeks to years or lifelong. It is prudent to review the neurosurgeon's operative note and the pathology report to assess the degree of normal pituitary gland resected. In general, the longer a patient requires steroid replacement, the better for assuring remission. If a patient is able to discontinue steroid replacement 1 to 3 months after surgery, the patient should be monitored closely for recurrence. The method of assessment to determine the need for steroid replacement varies, some endocrinologists recommend an ITT as the definitive test to assess hypothalamic–pituitary–adrenal reserve and GH deficiency and others advocate an ACTH test as an adequate measure to assess the need for chronic steroid replacement. Whereas the ITT is the more definitive study, the ACTH stimulation test is probably adequate if performed 2 to 3 months after surgery and off steroid replacement for 3 to 7 days. An alternative method of assessing the need for chronic steroid replacement is to discontinue the medication for a week or more, assess clinical symptoms, and measure early morning serum cortisol and ACTH levels. If these are normal, it is probably safe to discontinue steroid replacement and observe the patient. If a definitive test is not performed, then the patient should be given steroid therapy in the event of surgery or a significant illness, such as pneumonia or pyelonephritis. Regular follow up of patients with Cushing's disease is important to identify recurrence and the need for additional treatment. Patients in remission from Cushing's disease will be the first to recognize a recurrence, commonly fatigue, depression, difficulty sleeping, and weight gain. If a patient reports symptoms of recurrence, the patient is usually correct and measurement of the 24-hour UFC level is indicated. This may be normal initially, but with subsequent measurements over time, the UFC usually becomes elevated. The important concept is that any patient with a history of Cushing's disease is at risk for recurrence and usually identifies the problem early and before obvious clinical features develop. If the UFC is elevated, an MRI study is indicated. Subsequent treatments, depending on the MRI findings, include a second surgery and pituitary radiation (conventional, Gamma knife, proton beam, LINEAC) with medical treatment with ketoconazole or metyrapone or bilateral adrenalectomy. Adrenalectomy is usually reserved for patients who do not wish to have another pituitary surgery, who are intolerant of medical therapy, or who have not responded to radiation treatment within 2 years or more after treatment. Removal of the adrenal glands does pose the risk for developing Nelson's syndrome (20%–40%) and the patient should be informed of this possibility.

The result of surgery in patients with acromegaly is best assessed at least 6 weeks and sometimes longer after the operation. Because serum IGF-1 levels may remain elevated 3 or more months after surgery, it is not appropriate to measure this hormone immediately after the operation. The definitive test to assess GH secretion is the 2-hour oral glucose tolerance test

with measurement of serum GH every 30 minutes over 2 hours (a single or 2 GH levels after oral glucose is not appropriate or adequate). Using contemporary criteria, remission of acromegaly is defined as a glucose suppressed GH of less than 1 ng/mL (ug/L) and a normal serum IGF-1 for age and sex. The previously considered indicators of remission, serum GH of less than 5 or greater than 10 ng/mL (μg/L), are no longer applicable with more sensitive GH assays. Improvement in clinical features of acromegaly should include a decrease in soft tissue swelling (face, hands, and feet), improvement in hyperhidrosis, sleep apnea, hypertension, and diabetes mellitus if present. If the GH response to oral glucose is greater than 1 ng/mL (μg/L) then the patient has persistent acromegaly that needs additional treatment, medical therapy and pituitary radiation as indicated by the severity of disease and the patient's decision.

In patients with a prolactinoma, a normal serum prolactin after surgery is the optimal response. Return of normal gonadal function is the clinically important corollary to successful surgery. Resumption of cyclic menses in premenopausal women and return of normal sexual function and a normal serum testosterone level in men are the optimal responses to surgery. If return of normal gonadal function does not occur, then gonadal steroid replacement is indicated.

Replacement therapies

If the pituitary lesion or the consequence of surgery results in hypopituitarism, the deficient hormones should be replaced as physiologically as possible. Replacement of thyroid hormone, testosterone, and growth hormone can easily be monitored by measurement of serum thyroxine or free T_4, testosterone and IGF-1 concentrations to determine the appropriate dose. There are no accurate tests to assess the adequacy of glucocorticoid and desmopressin replacement; these require clinical assessment for optimal dose adjustment. What was previously thought to be "physiologic" hydrocortisone replacement, 20 mg on awakening and 10 mg in the late afternoon, was shown to cause significant loss of bone mass. Currently, the usual hydrocortisone replacement dose is 15 mg on awakening and 5 mg in the late afternoon. The longer acting glucocorticoid, prednisone, is a suitable alternative with the usual dose of 5 mg on awakening and 2.5 mg in the late afternoon and some patients may be adequately replaced with a single morning dose of 5 mg. Symptoms of inadequate steroid replacement include fatigue in the evening and headache on awakening relieved by taking hydrocortisone or prednisone, indicating the need for an evening dose or an increased evening dose. Optimal desmopressin replacement is best assessed clinically—the patient can usually report at the time the medication ceases to be effective—the onset of urinary frequency and thirst are accurate indicators of the need for an additional desmopressin dose. Because some patients can be controlled with a once daily dose and others require a dose

every 12 hours, adjustment of the dose should be made by urinary frequency. Periodic measurement of serum sodium is indicated to detect hyponatremia (a patient with an intact thirst center will drink adequate fluid and rarely develops hypernatremia).

Summary

The management of a patient who requires pituitary surgery should be a constant collaboration between the neurosurgeon and the endocrinologist. Because the pituitary gland is an anatomic and functional entity, both medical specialties are necessary to treat these patients for the best possible outcome.

The notion that pituitary surgery is always curative is not accurate because of the risk for tumor recurrence. A patient with a pituitary lesion who undergoes surgery is clinically identical to a patient with diabetes mellitus—these patients require lifelong monitoring and management as indicated by the clinical, endocrine and anatomic findings. Because there is always a risk for tumor recurrence, appropriate surgical or radiation treatment and hormone replacement may be required at any time after the initial operation. In the patient who undergoes postoperative pituitary radiation, the risk for developing a new pituitary hormone deficiency ranges from 33% to 50%, and is probably higher over time. Thus, these patients must receive regular evaluations regarding the need for additional treatment and hormone replacements.

A regular program of life long assessment of pituitary function and anatomy, appropriate hormone replacement and close collaboration with a pituitary surgeon is the ideal care of these patients. Only with such a program can a patient with a pituitary adenoma achieve the best possible outcome.

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